IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Kolter et al.	Docket No.:	51284
Serial No.:	09/811,546	Confirmation No.:	9100
Filing Date:	3/20/2001	Examiner:	SILVERMAN, ERIC E
Customer No.:	26474	Art Unit:	1615

For: Solid oral dosage forms with delayed release of active ingredient and high mechanical stability

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Appeal brief under 37 C.F.R. § 41.37

Sir:

This is an appeal from the Examiner's final rejection of claims 1, 3 – 19 and 21 – 24, mailed February 26, 2007. A notice of appeal was filed June 26, 2007.

The fee set forth in 37 C.F.R. § 41.20(b)(2) is paid by credit card. Form PTO-2038 is enclosed. Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees, to Deposit Account 14.1437. Please credit any excess fees to such account.

Respectfully submitted,
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Date: August 23, 2007

Real party in interest:

The real party in interest is BASF Aktiengesellschaft, of Ludwigshafen, Germany.

Related appeals and interferences:

To the best of the undersigned's knowledge, there are no related interferences or judicial proceedings.

Status of claims:

- Claims 1, 3 – 19 and 21 – 27 are currently pending.
- Claims 1, 3 – 19 and 21 – 24 stand rejected.
- Claims 2 and 20 are canceled.
- Claims 25 and 26 are withdrawn.
- Claims 1, 3 – 19 and 21 – 24 and 27 are being appealed.

Status of amendment:

No claim amendment was filed after the final rejection mailed February 26, 2007.

Summary of claimed subject matter:

The independent claim involved in the appeal is claim 1. All other appealed claims are dependent on claim 1. Summary of the subject matter of the dependent claims is omitted as unnecessary.

Independent claim 1 relates to an oral dosage form with delayed release of active ingredient and high mechanical stability.[1] The inventive dosage form comprises

a) one or more active ingredients;[2]

b) a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone;[3]

c) water soluble polymers or lipophilic additives;[4] and

d) other conventional excipients.[5]

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[1] Page 1, lines 1 – 2 of the Specification.
[2] Page 5, line 1 of the Specification.
[3] Page 5, lines 3 – 4 of the Specification.
[4] Page 5, lines 6 – 7 of the Specification.
[5] Page 5, line 9 of the Specification.

The formulated mixture of polyvinyl acetate and polyvinylpyrrolidone facilitates the delayed release.[6] The formulated mixture of polyvinyl acetate and polyvinylpyrrolidone comprises from 20 to 80% of the total weight of the dosage form.[7] The ratio of polyvinyl acetate to polyvinylpyrrolidone is from 6:4 to 9:1.[8]

The examples of the specification further support the term "delayed release" by showing (1) that at most 25.3% of active ingredient is released after 1 hour,[9] and (2) that typically only 64.4% of active ingredient is released after 16 hours.[10] The specification also makes clear that "[t]he formulated mixture of polyvinyl acetate and polyvinylpyrolidone is … an intimate mixture of a lipophilic with a hydrophilic polymer…."[11]

Grounds of rejection to be reviewed on appeal

Whether the examiner erred in rejecting claims 1, 3 – 19, and 21 – 24 under 35 U.S.C. §103(a) over Kolter et al. (US 6,066,334) in view of Ortega (US 4,837,032).

Argument

"Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved."[12]

The Kolter et al. reference is directed to "the use of redispersible polymer powders or polymer granules consisting of polyvinyl acetate and N-vinylpyrrolidone-containing polymers as binders for producing solid pharmaceutical presentations."[13] Kolter et al. make clear that "the binder content in the presentation is to be less than 20% by weight."[14] Finally, the reference stresses that the pharmaceutical presentations prepared according to the invention "make rapid release of the active ingredients

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[6] Page 3, lines 17 – 46 of the Specification.
[7] Page 7, lines 26 – 29 of the Specification.
[8] Page 7, lines 31 – 32 of the Specification.
[9] SEE: Table 12.
[10] SEE: Tables 2, 8 and 10.
[11] Page 3, lines 17 – 21 of the specification.
[12] Graham v. John Deere, 383 U.S. 1, at 17 – 18, 148 USPQ 459 (1966).
[13] Column 1, lines 6 – 9 of US 6,066,334.
[14] Column 2, lines 19 – 20 of US 6,066,334.

possible."[15]

The Ortega reference relates to sustained release tablets of a particular pharmaceutical, theophyline. "The controlled steady release is achieved by means of a polymeric matrix from which the tablet is formed. Because of its composition, the tablet tends to swell and slowly erode rather than disintegrating."[16] The Ortega tablet comprises "a water insoluble polymer, a polymer having carboxylic groups which is acid insoluble but dissolves in neutral or alkaline medium, a water soluble or a swellable hydrophilic gel forming polymer and optionally a hydrophobic lubricant."[17] Ortega discloses that:

- "[t]he preferred [water insoluble] polymer is polyvinyl acetate, preferably at levels of 10 to 20 weight percent of the tablet[,]"[18]
- "[t]he preferred [acid insoluble] material is cellulose acetate phthalate at levels of 5 to 15 weight percent[,]"[19] and
- "[t]he preferred [water soluble] material is polyvinyl pyrrolidone at levels of 10 to 15 weight percent...."[20]

On the basis of these disclosures, the examiner argues that "[i]t would have been obvious to one of ordinary skill in the art to use increased amounts of a polymer combination of polyvinyl acetate and polyvinyl pyrrolidone to provide delayed release of an active agent."[21] Contrary to the examiner's assertion, a person of ordinary skill in the art would not have reduced the Ortega reference to a "teaching that the release rate can be altered by changing the amounts of binders, and that this is desirable to do in order to treat certain types of conditions or when using certain types of active ingredients."[22] A skilled artisan would have understood that the Ortega reference relates to sustained release tablets of a particular pharmaceutical, comprising not only a water insoluble polymer, and a water soluble or a swellable hydrophilic gel forming polymer, but also a

[15] Column 2, lines 21 – 22 of US 6,066,334.
[16] Column 2, lines 56 – 59 of US 4,837,032.
[17] Column 2, lines 63 – 68 of US 4,837,032.
[18] Column 3, lines 34 – 36 of US 4,837,032.
[19] Column 3, lines 46 – 47 of US 4,837,032.
[20] Column 3, lines 53 – 55 of US 4,837,032.
[21] Page 5, of the Office action mailed June 30, 2005.
[22] Page 6 of the Office action mailed July 03, 2006.

polymer having carboxylic groups which is acid insoluble but dissolves in neutral or alkaline medium. A skilled artisan would not have stripped away the complex and specific teachings of Ortega to conclude that increased amounts of polyvinyl acetate and polyvinyl pyrrolidone provide delayed release of an active agent. Such a principle, while simple and devoid of subtlety, does not reflect what a skilled artisan would learn from the Ortega reference.

The present invention is directed to an oral dosage form with delayed release of active ingredient and high mechanical stability, comprising a) one or more active ingredients; b) from 20 to 80%, based on the total weight of the dosage form, of a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone; c) water soluble polymers or lipophilic additives; and d) other conventional excipients, wherein the ratio of polyvinyl acetate to polyvinylpyrrolidone is from 6:4 to 9:1 and said formulated mixture of polyvinyl acetate and polyvinylpyrrolidone facilitates said delayed release.

The examiner has asserted that no patentable weight is given to the phrase "dosage form with delayed release," merely because the phrase is in the preamble to the claim. In the Advisory action mailed June 11, 2007, the examiner stated, "[w]hile Applicant is correct that the preamble may be afforded patentable weight in some circumstances, in this case, the claims do not require the preamble to breath[e] life and ... meaning to them." As was pointed out in the reply to the final Office action mailed February 26, 2007, "[t]he determination of whether a preamble limits a claim is made on a case-by-case basis in light of the facts in each case; there is no litmus test defining when a preamble limits the scope of a claim."[23] However, "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention...."[24] Applicants have clearly relied on the preamble during prosecution to distinguish from the cited references, thus the examiner's refusal to "afford patentable weight" to the preamble is in error.

Moreover, the preamble of claim 1, "An oral dosage form with delayed release of active ingredient ..." when read in the context of the entire claim clearly recites a

[23] MPEP § 2111.02, citing Catalina Mktg. Int'l v. Coolsavings.com, Inc., 289 F.3d 801, 808, 62 USPQ2d 1781, 1785 (Fed. Cir. 2002).
[24] Catalina Mktg. Int'l v. Coolsavings.com, Inc., 289 F.3d at 808-09, 62 USPQ2d at 1785.

limitation of the claim. Thus, even if applicants had not clearly relied on the preamble during prosecution, the claim preamble should be given patentable weight. "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim."[25] The examiner has erred in cursorily characterizing this limitation as a "recitation of intended use," because "[t]he determination of whether preamble recitations are structural limitations or mere statements of purpose or use 'can be resolved only on review of the entirety of the [record] to gain an understanding of what the inventors actually invented and intended to encompass by the claim.'"[26]

Next, the claims require a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone. The specification makes clear that "[t]he formulated mixture of polyvinyl acetate and polyvinylpyrolidone is ... an intimate mixture of a lipophilic with a hydrophilic polymer...."[27] Thus, "[t]he formulated mixture of polyvinyl acetate and polyvinylpyrolidone is ... more suitable for release slowing ...."[28] By formulating PVP and PVAc together prior to admixing the formulated mixture with the other components an intimate mixture of the two copolymers is formed. For completeness sake, it is noted that the distinctive release patterns of the present invention are due to the formulation of the dosage forms and the choice of amounts used in the overall mixture not only to the presence of the formulated mixture of polyvinyl acetate (PVAc) and polyvinylpyrrolidone (PVP).

Against this background of the scope and content of the prior art, the differences between the prior art and the claims; and the level of ordinary skill in the pertinent art the nonobviousness of the subject matter is clear.

The Kolter et al. reference is directed to "[a] solid, rapid release, pharmaceutically active composition, from which the active ingredients are released within a time of from

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[25] *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999).
[26] MPEP § 2111.02, citing Corning Glass Works, 868 F.2d at 1257, 9 USPQ2d at 1966.
[27] Page 3, lines 17 – 21 of the specification.
[28] Page 3, lines 17 – 21 of the specification.

0.1 to 1 hour, as measured in simulated gastric acid."[29] The present invention relates to an oral dosage form with delayed release of active ingredient. The specification makes clear that "delayed release" is far different than what is described in the Kolter et al. reference, because the present specification shows (1) that at most 25.3% of active ingredient is released after 1 hour,[30] and (2) that typically only 64.4% of active ingredient is released after 16 hours.[31] Thus, in order to start from the Kolter et al. reference and arrive at the present invention, a skilled artisan would need to change the principle of operation of the Kolter et al. reference by changing from a rapid release composition to a dosage form with delayed release of active ingredient. It is well-settled that "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious."[32]

To refute the fact that a change in the principle of operation would be required, the examiner argues that "Kolter teaches a range of release times"[33] and that Ortega teaches "how to optimize the release profile."[34] A skilled artisan would not share the examiner's interpretation. Kolter et al. teaches a very narrow range of immediate release times. The Ortega reference has nothing to do with the "optimization" of immediate release times. To the contrary, the Ortega reference relates to sustained release tablets of a particular pharmaceutical, comprising not only a water insoluble polymer, and a water soluble or a swellable hydrophilic gel forming polymer, but also a polymer having carboxylic groups which is acid insoluble but dissolves in neutral or alkaline medium.

Indeed, the cited references provide no "apparent reason to combine known elements in the fashion claimed ...."[35] A skilled artisan would not have stripped away the complex and specific teachings of Ortega to conclude that increased amounts of polyvinyl acetate and polyvinyl pyrrolidone provide delayed release of an active agent, and would have found the actual teachings of Ortega inapplicable to Kolter et al. Moreover, neither Ortega nor Kolter et al. disclose a formulated mixture of PVP and

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[29] Claim 1 of US 6,066,334.
[30] SEE: Table 12.
[31] SEE: Tables 2, 8 and 10.
[32] MPEP §2143.01, citing In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)
[33] Page 4, line 5 of the Office action mailed February 26, 2007.
[34] Page 4, line 6 of the Office action mailed February 26, 2007.
[35] *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ___ (2007), Slip op. at 14, 127 S.Ct. 1727 at 1741.

PVAc as required by the present claims. The specification makes clear that by formulating PVP and PVAc together prior to admixing the formulated mixture with the other components, an intimate mixture of the two copolymers is formed, and that "[t]he formulated mixture of polyvinyl acetate and polyvinylpyrolidone is … more suitable for release slowing …."[36] For at least these reasons, the present invention is not obvious over Kolter et al. in view of Ortega.

In conclusion, the examiner erred by rejecting claims 1, 3 – 19, and 21 – 24 under 35 U.S.C. §103(a) over Kolter et al. (US 6,066,334) in view of Ortega (US 4,837,032). The rejection should be reversed. Favorable action is requested.

[36] Page 3, lines 17 – 21 of the specification.

Claims appendix.

1. (previously presented) An oral dosage form with delayed release of active ingredient and high mechanical stability, comprising
   a) one or more active ingredients
   b) from 20 to 80%, based on the total weight of the dosage form, of a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone
   c) water soluble polymers or lipophilic additives
   d) and other conventional excipients,
   wherein the ratio of polyvinyl acetate to polyvinylpyrrolidone is from 6:4 to 9:1 and said formulated mixture of polyvinyl acetate and polyvinylpyrrolidone facilitates said delayed release.

2. (canceled)

3. (previously presented) An oral dosage form a claimed in claim 1, wherein a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone in the ratio 8:2 is employed.

4. (previously presented) A oral dosage from as claimed in claim 1, which is a tablet, extrudate, pellet or granulate.

5. (previously presented) An oral dosage form as claimed in claim 1, wherein a water-soluble or water-insoluble release-delaying coating is applied to the oral dosage form.

6. (previously presented) An oral dosage form as claimed in claim 1, wherein the water-soluble or lipophilic polymers are selected from the group consisting of: polyvinyl alcohols, polyethylene glycols, polyoxyethylene/polyoxypropylene block copolymers, polyvinylpyrrolidones and derivatives, and vinyl acetate/vinylpyrrolidone copolymers.

7. (previously presented) An oral dosage form as claimed in claim 1, wherein the water-soluble swelling polymers are selected from the group consisting of: alginates, pectins, galactomannans, carrageenans, dextran, curdlan, pullulan, gellan, chitin, gelatin, xanthans, hemicelluloses, cellulose derivatives and starch and salts thereof.

8. (previously presented) An oral dosage form as claimed in claim 1, wherein the lipophilic additives are selected from the group consisting of: cellulose derivatives, acrylic ester/methacrylic ester copolymers, fatty alcohols, fatty acids, fatty acid esters and fatty alcohol esters, glycerides, waxes, and lecithin.

9. (previously presented) An oral dosage form as claimed in claim 1, which is produced by direct compression, extrusion, melt extrusion, pelleting, compaction, wet granulation.

10. (previously presented) An oral dosage form as claimed in claim 1, wherein the conventional excipient comprises:

binder, extenders/fillers, disintegrants, lubricants, flow regulators, dyes, or stabilizers.

11. (previously presented) An oral dosage as claimed in claim 1, wherein the formulated mixture of polyvinyl acetate and polyvinylpyrrolidone is present in a proportion of from greater than 20% to less than or equal to 80% based on the total weight of the dosage form.

12. (previously presented) An oral dosage form as claimed in claim 1, wherein the water-soluble polymers and/or the lipophilic additives are present in a proportion of from 1 to 40% based on the total weight of the dosage form.

13. (previously presented) An oral dosage form as claimed in claim 1, wherein hydroxypropylmethylcellulose are employed as water-soluble polymers.

14. (previously presented) An oral dosage form as claimed in claim 1, wherein in polyvinylpyrrolidones or vinyl acetate/vinylpyrrolidone copolymers are employed was water-soluble polymers.

15. (previously presented) An oral dosage form as claimed in claim 1, which is a press-coated tablet whose core is rich in active ingredient.

16. (previously presented) An oral dosage form as claimed in claim 1, which comprises as active ingredients food supplements or additives, vitamins, minerals or trace

elements or active pharmaceutical ingredients.

17. (previously presented) An oral dosage as claimed in claim 1, which comprised active pharmaceutical ingredients as active ingredients.

18. (previously presented) The dosage form as claimed in claim 1, wherein the active pharmaceutical ingredient is selected from the group consisting of benzodiazepines, antihypertensives, vitamins, cytostatics, anesthetics, neuroleptics, antidepressants, antibiotics, antimycotics, fungicides, chemotherapeutics, urologicals, platelet aggregation inhibitors, sulfonamides, spasmolytics, hormones, immunoglobulins, sera, thyroid therapeutics, psychopharmaceuticals, antiparkinson agents and other antihyperkinetics, ophthalmologicals, neuropathy products, calcium metabolism regulators, muscle relaxants, lipid-lowering agents, liver therapeutics, coronary agents, cardiac agents, immunotherapeutics, regulatory peptides and their inhibitors, hypnotics, sedatives, gynecologicals, antigout agents, fibrinolytics, enzyme products and transport proteins, enzyme inhibitors, emetics, perfusion promoters, diuretics, diagnostics, corticoids, cholinergics, biliary therapeutics, antiasthmatics, bronchospasmolytics, beta-receptor blockers, calcium channel blockers, ACE inhibitors, arteriosclerosis remedies, antiinflammatory agents, anticoagulants, antihypotensives, antihypoglycemics, antifibrinolytics, antiepileptics, antiemetics,

antidotes, antidiabetics, antiarrhythmics, antianemics, antiallergics, anthelmintics, analgesics, analeptics, aldosterone antagonists, and weight-reducing agents.

19. (previously presented) A drug for delayed release of active ingredients, which is an oral dosage form as claimed in claim 1.

20. (canceled)

21. (previously presented) Food supplements or additives, or vitamins, minerals or trace elements comprising the oral dosage form as claimed in claim 1 for delayed release of active ingredients.

22. (previously presented) An oral dosage form as claimed in claim 6 wherein the water-soluble or lipophilic polymers are selected from the group consisting of polyethylene glycols, polyvinylpyrrolidones, vinyl acetate/vinylpyrrolidone copolymers or maltodextrins, and salts thereof.

23. (previously presented) The oral dosage form as claimed in claim 7, wherein the cellulose derivatives are selected from the group consisting of methylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose and wherein the starch derivatives are selected from the group consisting of carboxymethyl starch, degraded starch, polyacrylic acid, polymethacrylic acid, acrylic acid/methacrylic acid copolymers.

24. (previously presented) The oral dosage form as claimed in claim 8, wherein the lipophilic additives are selected from the group consisting of cellulose derivatives which are ethylcellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate succinate, hydroxy propylmethylcellulose acetate phthalate, or hydroxypropylmethylcellulose acetate succinate, acrylic ester/ethacrylic ester copolymers which are methyl methacrylate/ethyl acrylate copolymers, ammoniomethacrylate copolymer type A and type B, methacrylic acid/acrylic ester copolymers or methacrylic acid/ethyl acrylate copolymers, fatty alcohols which are stearyl alcohols, fatty acids which are stearic acid, fatty acid esters and fatty alcohol esters, glycerides, waxes and lecithin.

25. (withdrawn) A method for making an oral dosage form with delayed release of active ingredient and high mechanical stability by processing an oral dosage form with delayed release of active ingredient and high mechanical stability, comprising combining

a) one or more active ingredients

b) from 20 to 80%, based on the total weight of the dosage form, of a formulated mixture of polyvinyl acetate and polyvinylpyrrolidone

c) water soluble polymers or low or high molecular weight lipophilic additives

d) and other conventional excipients,

wherein the ratio of polyvinyl acetate to polyvinylpyrrolidone is from 6:4 to 9:1 and said

formulation facilitates said delayed release.

26. (withdrawn) The method for making an oral dosage form with delayed release of active ingredient and high mechanical stability by processing an oral dosage form with delayed release of active ingredient and high mechanical stability of claim 25 further comprising a step selected from the group consisting of melt extrusion, film coating and press coating.

27. (new) An oral dosage form as claimed in claim 1, wherein the stabilizer comprises an antioxidant, a wetting agent, a preservative, a release agent, a flavoring or a sweetener.

Evidence appendix

None.

Related proceedings appendix

None.